

REMARKS

Applicants thank the Examiner for thorough consideration given the present application.

Claims 94-96 and 98-117 are pending in this application. Claims 96, 101 and 106-116 have been withdrawn. Claims 98 and 99 have been amended. No new matter has been added. For instance, amended claim 98 is supported by at least pages 53 and 54 of the present specification. New claim 117 is supported by claim 99. Thus, no new matter is introduced.

In light of remarks set forth below, reconsideration and withdrawal of all outstanding rejections are respectfully requested.

Issues under 35 USC § 112, first paragraph

The Examiner has rejected claims 94, 95, 98-100 and 102-105 under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement with respect to use of certain glycoconjugates. Also, the Examiner has rejected claim 98 under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement with respect to insufficient coverage of “less than 180°C”. These rejections are respectfully traversed.

Regarding claims 94, 95, 98-100 and 102-105, the Examiner asserts that although the specification is enabling for making glycoconjugates having a well-known utility, it does not reasonably provide enablement for the scope of glycoconjugates made by the present method. Applicants respectfully disagree with this assertion. In particular, the Examiner appears to believe that those of skilled in the art are not taught how to use the products made by the present method.

However, the U.S. publication of the present application clearly discloses how to use the product prepared by the present method. As shown in the following paragraphs, the glycoconjugates prepared by the present method can be used for improving human gastrointestinal health, for food and drinks, and for marking products as follows.

Food/human gastrointestinal application

[199] *The invention aims to produce variety of carbohydrates which are needed for **human gastrointestinal health**, these carbohydrates are not well exploited as these are in general not available in bulk scale. The present methods also allow more effective synthesis of the type of products which are commercially available.* (emphasis added)

[0202] ... *The arabinose oligosaccharide fractions are also expected to comprise special bioactive oligosaccharides especially related to **plant glycoconjugates active in human gastrointestinal trac** ...* (emphasis added)

Glycan libraries for marking products and food or drink applications

[0166] *The present invention is also directed to **the use of the mass finger prints to mark different products**. ... The compositions should be acceptable and are especially aimed at **additives for valuable foods or especially drinks.... The invention is also aimed at labelling products batchwise with different finger prints, which is useful for quality control.*** (emphasis added)

[0357] *The heterogenous saccharide mixture sets especially containing saccharides of having same molecular weights are **especially preferred for use in mass finger prints according to the invention to mark different products...*** (emphasis added)

Especially, the fingerprint analysis is performed by mass spectrometric profiling as shown in the Examples of the present application and this use is thus well demonstrated by the

present invention. Therefore, there is no doubt that the present carbohydrates may be applied for this use by artisan in the art without undue experimentation.

Further, various uses of the present oligosaccharide mixtures are well known to a person skilled in the art.

Glycan libraries for marking products

As explained above, the present material could be applied for this use very easily by any person of skill in the art.

Food/Gastrointestinal applications

The glycoconjugates made by the method of the present invention can be applied for production of food carbohydrate composition which can be accepted *with GRAS* status similarly as other heterogenous new carbohydrates previously.

GRAS status of novel compositions

The Examiner further indicates at page 8 of the outstanding Office Action that the present materials would be possibly toxic and not recognized as GRAS (safe) status. There is no doubt that novel carbohydrate materials not known to regulatory authority such as the FDA do not have GRAS status. However, there is no evidence as to why such GRAS status could not be obtained for the product prepared by the present method.

Applicants are of opinion that the product prepared by the present method will have GRAS approved like other similar approved products. In this respect, the Examiner has not provided any evidence as to why Applicants' product cannot be approved. For example, a skilled person in the art knows well how materials disclosed by Tibor Mora have been used with respect to nutrition. Random glucose oligomers with polyols and citrate are known as polydextrose or

"Litesse", with a trademark of Danisco. This material of Tibor Mora contains unnatural linkages similar to carbohydrate molecules of present invention. Tibor Mora's material was new at the time of synthesis and did not obviously have GRAS status at that time. However, in contrast to the reasoning of the Examiner, this material of Tibor Mora was found to be safe and has accepted for numerous food applications. Also, a wide range of galactooligosaccharides (GOS) produced by enzymatic transglycosylation currently exist. Further, it is known that such GOS materials contain numerous non-natural structures in random order, even though that they are known and accepted as safe.

Moreover, Applicants respectfully submit that when the present materials are used in gastrointestinal/food, a skilled person would expect the GRAS status indicating properties as follows:

I. Relatively good safety profile

The present materials are substantially same as natural oligosaccharides such as human milk oligosaccharides or commercial polydextrose (Litesse TM) and/or galacto-, manna-, xylo-, chitin, or arabinose oligopolysaccharide products. It is noted that there has been no reported that an oligosaccharide material comprising natural monosaccharide residues as in the present invention would be toxic or harmful. Also, numerous beneficial effects have been reported and known. In case there has been found no other beneficial effect, the present materials can be used for weight control as non-digestible fiber.

2. Low degradation and absorption from GI tract

Human milk oligosaccharides or other oligosaccharide materials are known to be quite stable in gastrointestinal tract. Especially polydextrose (Litesse TM) produced by the method similar to the present material is stable. Furthermore, oligo- or polysaccharide materials are not known to be absorbed from gastrointestinal tract, and therefore they are not expected to have any direct systemic blood circulation effects. It is relatively easy for a skilled person to optimize the present materials for specific gastrointestinal uses. There are no expected problems in a manner that other types of materials such as protein or peptide products cause in regular gastrointestinal product development.

Based on the above disclosure, Applicants respectfully submit since the use of the claimed glycoconjugate is clearly disclosed in the present specification and is also well known to the relevant art, use would be evident to one of skilled in the art and would not require undue experimentation. This disclosure meets the standard provided by MPEP §2164(c) as follows:

If a statement of utility in the specification contains within a connotation of how to use, 35 U.S.C. 112 is satisfied and if one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph.

Therefore, the pending claims properly meet the enablement requirement provided by 35 U.S.C. 112, first paragraph.

Regarding claim 98, the Examiner asserts that although the specification is enabling for some temperatures less than 180°C (e.g., room temperature, 80°C, 150-160°C and 50°C), it is not reasonably enabling for all temperatures less than 180°C.

Applicants respectfully submit that the present specification at pages 53 and 54 supports various reaction temperatures ranging from 1°C to 180°C, as admitted by the Examiner. Further, working Examples of Methods A-F at page 88 of the present specification demonstrate sufficient reaction temperatures such as 50°C, 80°C and 150-160°C. Therefore, those of skill in the art would expect any temperatures within a temperature less than 180°C could be used in that manner without undue experimentation.

Nevertheless, based on the present specification at pages 53 and 54, claim 98 has been amended to recite “wherein the reaction is conducted at a temperature ranging from about 1°C to about 180°C”. By way of this amendment, this part of the rejection is moot.

Reconsideration and withdrawal of the 35 U.S.C. 112, first paragraph rejections are respectfully requested.

Issues under 35 USC § 112, second paragraph

The Examiner has rejected claims 99 and 102-104 under 112, second paragraph due to a certain indefiniteness. Also, the Examiner has rejected claims 103-105 under 112, second paragraph due to insufficient antecedent basis. These rejections are respectfully traversed.

Regarding claim 99, this claim uses the term “preferably”. Accordingly, Applicants added new claim 117 depending from claim 99 to cover a “polyol” while deleting “, preferably a polyol” from claim 99.

Regarding claim 102, this claim uses the terms “bitter taste” and “undesired color”, in which the Examiner sees them as “relative”. However, Applicants respectfully submit that the specification provides the relevant disclosures. Specifically, page 4, lines 33-35 of the present

specification discloses that the bitter taste or undesired color of the reacting products comes from anhydro forms of glucose, especially the ester. Also, it is well known that one of skill in the art can understand what these terms mean.

Regarding claims 103-105, the Examiner has indicated at page 15 of the outstanding Office Action that a mixture or library of oligosaccharides or polysaccharides in these claims fails to have an antecedent basis because claim 94 does not recite a method of preparing a mixture of multiple oligosaccharides or polysaccharides. However, Groups F and G of claim 94 recite oligosaccharides and polysaccharides, respectively, and claim 94 requires that at least two non-protected saccharides are reacted. Therefore, by following the method of claim 94, a mixture or library of oligosaccharides or polysaccharides can be obtained.

As discussed above, by way of the present submission, reconsideration and withdrawal of the 112, second paragraph rejections are respectfully requested.

Issue under 35 USC § 103(a)

The Examiner has rejected claims 94, 95, 98-100 and 102-105 under 35 USC § 103(a) as obvious over Kanie et al. (Solid Support Oligosaccharide Synthesis and Combinatorial Carbohydrate Libraries, 2001, p239-256) in view of Rennhard (USP 3,766,165) and further in view of Tibor Mora et al. (USP 2,719,179). These rejection are respectfully requested.

The Present Invention and Its Advantages

The present invention of claim 94 is directed to a method for the preparation of glycoconjugates comprising reacting under condensing conditions involving acid or metal

catalysis at least two non-protected saccharides selected from the group consisting of: A. aldomonosaccharides, B. deoxyhexoses, C. N-acetyldoses, D. sialic acids, E. hexuronic acids, H. oligosaccharides containing a saccharide from any one of groups A – E, G. polysaccharides containing a saccharide from any one of groups A – E, so that said saccharides are selected from at least two of groups A – G; in order to form a glycosidic bond between said saccharides through any free hydroxyl group position in said saccharides, wherein C1-positions of the reacting saccharides are not protected. The present invention is mainly directed to the use of non-protected carbohydrates, such as monosaccharides, oligosaccharides and polysaccharides. The use of non-protected carbohydrates makes the process much more cost-effective and gives high variability in the carbohydrate libraries to be produced.

The Distinctions between the Present Invention and the Cited Art

Kanie discloses reactions of traditional protected and activated monosaccharides with nonprotected acceptors in polar organic chemistry solvents and production of oligomers of various monosaccharide types. However, Kanie does not provide any evidence that similar reactions would occur if:

- 1) the donor monosaccharides were not activated;
- 2) the donor monosaccharide was not protected, or more specifically not protected by benzyl groups, it is especially known that also other protection status affects donor reactivity with the activated monosaccharides;
- 3) acid or heat catalysis is used in dry or aqueous environment.

Thus, Kanie cannot be expected from the claimed invention.

Also, the deficiencies of Kanie cannot be remedied by Tibor Mora and Rennhard because these cited references fail to disclose or suggest any reactivity of different monosaccharide types or any reactivity under Kanie conditions. Thus, a combination of the cited art cannot be made.

In this context, it is respectfully submitted the Examiner's combination does not consider the problems caused by combining different reaction conditions and substrates and selecting from all possible combinations of Kanie with Rennhard and Tibor More. Specially, Kanie's reaction is in the field of regular organic chemistry and cannot give any prediction of the reactions on non-protected saccharides under Rennhard/Tibor Mora conditions. Similarly, Rennhard and Tibor More's reaction conditions and reagents do not include the claimed monosaccharide types and does not give any prediction of success if they are applied to Kanie molecules or their non-protected variants.

Six hypothetical direct combinations of the cited prior art might be as follows:

- 1) Rennhard/Tibor Mora reaction conditions and Rennhard/Tibor Mora solvent/dry feature and Kanie molecules with activation and protection;
- 2) Rennhard/Tibor Mora conditions and Kanie solvent feature and Kanie molecules with activation and protection;
- 3) Rennhard/Tibor Mora conditions and Kanie solvent feature and Rennhard/Tibor Mora substrates;
- 4) Kanie reaction conditions, and Kanie solvent feature and Rennhard/Tibor Mora substrates;
- 5) Kanie reaction conditions and Rennhard/Tibor Mora solvent/dry feature and Kanie molecules with activation and protection; and

6) Kanie reaction conditions and Rennhard/Tibor Mora solvent/dry feature and Rennhard/Tibor Mora substrates.

However, instead of any combination of the above, the Examiner rather selects the following combination.

7) Rennhard/Tibor Mora reaction conditions and Rennhard/Tibor Mora solvent/dry feature and Kanie substrates modified to be a non-protected form like Rennhard/Tibor Mora by using such modification that since the number of possible modified method is at least four with respect to each of three parameters (reaction conditions either original two, or Kanie modified to Rennhard/Mora, or Rennhard/Mora modified to Kanie), this gives $4 \times 4 \times 4 = 64$ alternative combinations minus 2 original conditions (all Kanie or Rennhard/Mora) = 62 variations. From 62 variations, the Examiner selects the alternative which might have led to the present invention.

However, such a selection can be only based on hindsight and knowledge of the present invention. Considering taking only the Kanie protection or activation feature and difference of Rennhard and Tibor Mora, the actual amount of reaction possibilities to choose from would be extremely large. Further, due to the high level of unpredictability, most of them would be relatively useless, and in any *screening* efforts using all possible carbohydrates or carbohydrate reactable molecules (there is also conjugates in Kanie), the combination possibilities are endless without any specific expectations of success.

Furthermore, based on the cited art directed to their own conditions, the expected success on any original combinations or even worse modifications would be very low. There is no reason for an artisan to expect any special success without knowledge of the present invention.

As mentioned above, it is respectfully submitted that the Examiner has improperly employed hindsight reconstruction. The only basis for combining the cited references is that of hindsight reconstruction of Applicants' invention based solely on Applicants' disclosure. That is, the only basis to pick and choose the various features from each of the cited references is found nowhere but in Applicant's disclosure.

With regard to this, The Court of Appeals for the Federal Circuit has stated that to imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher. ... One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention. In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988) (quoting W.L. Gore Associates Inc. v. Garlock, Inc., 220 USPQ 303 (Fed. Cir. 1983)), Accord Grain Processing Corp. v. American Maize Prod. Co., 5 USPQ2d 1788 (Fed. Cir. 1988) ("care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit"); Panduit Corp. v. Dennison Mfg. Co., 1 USPQ2d 1593 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987); Orthopedic Equipment Co. v. United States, 217 USPQ 193 (Fed. Cir. 1983).

As discussed above, the present invention is not made obvious over the cited art individually as explained above. Also, a combination of the cited art is not possible and the present invention is patentably distinct from the combined teachings of the cited art.

Conclusion

In view of the above remarks, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Craig A. McRobbie Reg. No. 42,874 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By 

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